Please amend claim 12 as follows:

12. (Amended) The method as defined in claim 9 wherein said particles of such construct are less than about 10 microns in diameter.

Please amend claim 13 as follows:

13. (Amended) The method as defined in claim 10 wherein said construct comprises particles which are less than about 10 micrometers in diameter.

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Please amend claim 14 as follows:

14. (Amended) The method as defined in claim 11 wherein said particles of such construct are less than about 5 micrometers in diameter.

REMARKS

Claim 1-14 are presently in the subject application.

Claims 1 and 8 through 14 have been amended to more particularly define and more fully protect Applicants' invention. The amendments do not introduce new matter nor raise any new issues. Support for the amendments is found in the subject specification at page 13, lines 2-5; page 14, first full paragraph, and page 16, bridging paragraph to page 17, entire page. Additionally for inhalation therapy, the particle size is inherently less than about 10 microns. In this regard, reference is made to S. Purewal et al., "Metered Dose Inhaler Technology", page 13, (Figure 2-2) (1998) [a copy of which is enclosed herewith]; and Stephen P. Newman et al., "Aerosols in Medicine, Principles, Diagnosis and Therapy", Ch. 7, page 94, bridging paragraph and TABLE I (1985). Accordingly entry of these amendments is respectfully requested.

Claim 11 has been objected to because a range is not designated. Claim 11 has been amended whereby, as described in the specification and as is inherent in the inhalation art, less

than about or "under 10 microns in diameter", defines the particle size. Accordingly, claim 11 is not subject to an objection and should not "be interpreted to mean under 20 micrometers".

Additionally, the Examiner forwards that claim 11 is identical to claim 12. Amended claims 11 and 12 depend from **different** claims and are not identical and are not subject to an objection. A "solution" (claim 8) and a "dispersion" (claim 9) are not identical physical forms.

Claims 1 through 14 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, with respect to claim 1, the Examiner refers to the term "polymeric construct" and forwards that this term fails to particularly point and distinctly describe the metes and bounds. It is respectfully submitted that claim 1 is not subject to a rejection under 35 U.S.C. § 112, first paragraph, in the use of a "polymeric construct".

Firstly, applicants can be their own lexicographer in the use of the "polymeric construct" term to describe a vehicle or structure which, as the Examiner points out, encompasses (1) an "aerosol particles comprising polysaccharide vesicles" (page 3, line 4 of the subject specification); (2) a "polymeric construct particle" (page 12, line 23 of the subject specification); (3) a "gel-like structure" (page 14, line 5 of the subject specification); and (4) a suitable polymeric construct which is "one which will incorporate therein or encapsulate the selected medicament" (page 13, line 4 of the subject specification). One of ordinary skill in the art would readily recognize the scope, i.e., the metes and bounds, of claim 1.

Additionally, it is to be noted that at page 1, under "Field of the Invention", the Applicants have defined the subject matter of the invention. Specifically, it is stated that:

> This invention relates to modulated release aerosol particles and more particularly, to medicinal aerosol particles comprising **polymeric vesicles** which entrap a selected medicament and provide slow release thereof.

The term "polymeric vesicles" describes completely the metes and the bounds of the invention as one of ordinary skill in the art would readily attest. Vesicles are particulate bodies. Polymeric vesicles are particulate bodies which utilize a polymer as a linker or anchor in the architecture or structure of the particles. In the subject invention, polymeric medicament vesicles are polysaccharide-medicament matrixes of particles with size appropriate for inhalation. The term "polymeric construct" is generic to describe the polymer-medicament-particulate-matrix, which one of ordinary skill in the art would recognize as appropriate to encompass the vehicle claimed.

Accordingly, allowance of amended claim 1 as well as claims 2-14 is requested.

The Examiner forwards that claim 8 is indefinite in the recitation of "suitable anti-solvent". The term "suitable" has been deleted from amended claim 8, since, one of ordinary skill in the art would know which anti-solvent is suitable. Additionally, the term "anti-solvent" is well known and understood in the art.

The term anti-solvent is a universal technical term used to describe a fluid within which a dissolved substance would crystallize, precipitate, or separate out as a solid. It is the exact opposite of the term "solvent" which describes a fluid within which a substance may be dissolved so that is completely homogeneous with the fluid. The anti-solvent of claim 8 is any fluid that would cause the dissolved medicament to separate out of solution to result in the formation of solid, dry medicament vesicles. The choice of fluids in any particular case will depend on the nature of the substance from which particles are to be formed, on the anti-solvent fluid to be used in forming them, and on other **practical** criteria including those governing the desired end product. The choice of a suitable combination of fluids and vehicles for any desired product will be well within the capabilities of one of ordinary skill in the art, and may depend

generally on solubilizing, miscibility and polarity characteristics. This term is appropriate and not indefinite and the methodology disclosed in the subject application sufficiently and satisfactorily teaches the invention.

It is submitted that claim 8 as well as claim 11 and 14, which are also subject to a rejection under 35 U.S.C. § 112, first paragraph are not indefinite. Allowance of claim 8, as well as claims 11 and 14, is requested.

Claims 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, in the recitation of "a critical pressure and temperature". The Examiner is correct in stating that specifications on critical conditions may be necessary. However, the choice of fluids, including suitable combinations of the solvent and anti-solvent in any particular case, would depend on the nature of the medicament and on other **practical** criteria including those governing the desired end product, which would be evident and readily ascertainable by one of ordinary skill in the art. The choice among the possible combinations of fluids and vehicles for any desired product will be well within the capabilities of a person of ordinary skill in the art without an undue amount of experimentation, and may depend generally on solubilizing, miscibility and polarity characteristics. Thus, it is virtually impossible to list all ranges of critical pressures and temperatures for all the possible combinations of fluids. The medicaments disclosed and claimed are semi-polar to polar peptide and protein substances. Furthermore, the final products utilize non-polar to moderately polar fluids as vehicles, and as such one of ordinary skill in the art can readily set critical fluid requirements based on what is described.

Accordingly, claims 8, 9 and 12 are not indefinite and not subject to a rejection under 35 U.S.C. § 112, first paragraph. Allowance of claims 8, 9 and 12 is respectfully requested.

Claim 9 is rejected under 35 U.S.C. § 112, first paragraph in the recitation of "appropriate anti-solvent". The term "appropriate" has been deleted from amended claim 9 since one of ordinary skill in the art would know what is an "appropriate" anti-solvent. The discussion with respect to claim 8 and the term "anti-solvent" applies equally as well for claim 9 and is reiterated hereat. Accordingly, allowance of claims 9 and 12 is respectfully requested.

Claims 11-14 are rejected under 35 U.S.C. § 112, first paragraph, for lacking antecedent basis for "particles of such construct". Claims 11-14 have been amended whereby antecedent basis is present. Allowance of claims 11-14 is requested.

Claims 11, 12 and 14 are deemed by the Examiner to be vague and indefinite in the recitation of particles "under 10 or under 20 micrometers in diameter". As discussed above, for inhalation therapy the particle size of a construct, such as the medicinal construct claimed, is well established in the art as being less than about 10 micrometers. Certainly, this is a sufficient teaching and definition of the metes and bounds to one of ordinary skill in the art in the practice of inhalation therapy. Reference is again made to Purewal et al., *supra* and Newman et al., *supra*.

Amended claims 11, 12 and 14 are not subject to a rejection under 35 U.S.C. § 112, first paragraph, and allowance of these claims is respectfully requested.

Claims 1, 2 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Goosen et al., U.S. Patent Nos. 4,689,293 ("GOOSEN"). GOOSEN teaches a method for microencapsulating living cells within a biocompatible semi-permeable membrane which has an outer surface comprising negatively charged materials to provide long term *in vivo* survivability of the cells. GOOSEN provides for the use of biocompatible microcapsules suitable for implantation in a mammalian body comprising encapsulated viable tissue or individual cells

within a biocompatible semi-permeable membrane having a biocompatible negatively-charged surface.

The macromolecular core material of GOOSEN is surrounded by a biocompatible semi-permeable membrane that is permeable to small molecules for contact with the core material but is impermeable to the core material and to potentially deleterious large molecules. It is to be noted that the material to be encapsulated is suspended in a physiologically-compatible medium containing a water soluble substance which can be reversibly gelled to provide a temporary protective environment for the tissue. The medium is formed into droplets, which under changing conditions of temperature, pH or ionic environment form temporary spherical capsules, which after treatment with certain ionic species render the outer membrane selectively permeable to the influx of nutrients and oxygen and efflux of metabolic products to the cell. It is pointed out that GOOSEN teaches that the **biocompatible** nature of the semi-permeable membrane should allow the passage of such materials to and from the core to occur without inflammation or other adverse body response while the outer negatively-charged surface inhibits surficial cell growth, so that the membrane remains semi-permeable and effective for extended periods of time, typically from three to six months or longer (GOOSEN, Col. 2, line 64 to Col. 3, line 21).

It is submitted that the treatment disclosed in GOOSEN of polyamino microcapsules with a biocompatible base-reactive material that retains the overall biocompatible nature of the semi-permeable membrane and, more importantly, results in a negatively-charged outer surface which inhibits cell growth and, therefore, permits the semi-permeable membrane to retain its permeability and hence effectiveness over an extended period of time, is not anticipatory of the subject invention. Notably, GOOSEN teaches the development of a **biocompatible** semi-permeable membrane encapsulating a core material that consists of interpenetrating layers of

ionically-interacted biocompatible materials (GOOSEN, Col. 4, lines 55-57). The subject invention is not directed to the use of a semi-permeable membrane to modulate medicament release; rather the invention is directed to a controlled dissolution medicament containing construct as a whole which subsequently controls concentrations of the medicament in the body of a patient being treated with the medicament construct.

GOOSEN teaches that the particles must have semi-permeable membranes with overall wall thickness ranging from about 5 to about 20 .mu.m., the microcapsules themselves having a diameter in the range of about 50 to about 2000 .mu.m., preferably in the range of about 200 to about 1000 .mu.m. for microcapsules containing islets of Langerhans as the core materials (GOOSEN, Col. 4, lines 58-63). The subject invention involves particles that must be of respirable size, preferably under 10 .mu.m. in order to aid release of the medicament in the peripheral lung. GOOSEN teaches that the biocompatible semi-permeable membrane must be a hydrogel with overall water content within the membrane structure of at least about 20 wt%, which may vary up to about 90 wt%. Applicants' invention is directed to a particle construct which is suspended in a non-aqueous propellant fluid applicable to inhalation delivery (the subject specification at page 4, first full paragraph). Thus, GOOSEN does not reveal or hint at Applicants' invention as defined in claims 1, 2 and 6.

Claims 1, 2 and 6 are not anticipated by GOOSEN and allowance of these claims respectfully requested.

Claims 3-5 are rejected under 35 U.S.C. § 103(a) as being obvious by GOOSEN in view of Mathiowitz et al., J. Appl. Polymer Sci (1988) 35: 755-774 ("MATHIOWITZ"). It is respectfully submitted that claims 3-5 are not obvious in view of these references when each is taken alone or in combination.

The deficiencies of GOOSEN discussed above are reiterated hereat.

MATHIOWITZ teaches a hot melt method for creating biodegradable microspheres of poly[bis(p-carboxy phenoxy)propane anhydride] copolymerized with sebacic acid where aqueous-catalyzed degradation of the cross-linked **polyanhydride** polymer backbone is the primary mechanism for *in vivo* release of dyes and insulin. GOOSEN does not teach anything about *in vivo* release of peptides and proteins but stresses selective transfer of materials across a semi-permeable membrane. Like GOOSEN, the preparations of MATHIOWITZ are in aqueous media but require hydrolytic deactivation of the polymer to release the encapsulated material. Both GOOSEN and MATHIOWITZ reveal a method of sub-dermal implanation of **polyanhydride** microspheres to control the influx or efflux of substances into tissues using the principle of surface molecular interactions. GOOSEN teaches that the microsphere particles must have biocompatible semi-permeable membranes fabricated from hydrogels with overall water content at about 20 wt%, which may vary up to about 90 wt%. Again, it is stressed that the claimed construct is destined for a dissolution based method of modulating medicament release from respirable particles formulated with polysaccharides using non-aqueous propellant-based fluids administered to the peripheral lung of animals or humans.

Notably, the medicament release of the claimed construct differs, not relying upon biochemical reactivity between the polymer and medicament species as is the case of MATHIOWITZ, but rather the physical dissolution phenomena.

In addition, the carriers used in the respective formulations or constructs are functionally different. The claimed construct is destined for non-aqueous fluid carriers and not the carriers taught by GOOSEN and MATHIOWITZ, namely, aqueous formulations for injection that must be isotonic with body fluids.

Why would one of ordinary skill in the art combine a reference which teaches selective transfer of a material across a semi-premeable membrane (GOOSEN) with another reference which teaches degradation by hydrolysis to deliver a material, such as insulin, (MATHIOWITZ) to arrive at Applicants' invention. There is no motivation action to combine GOOSEN and MATHIOWITZ and the Examiner has not made a showing of the teaching or motivation to combine the references. A failure to make this showing lends to a failure to establish obviousness, *In re Dembriczak*, 50 U.S.P.Q. 2d 1614, 1616-18 (Fed. Cir. 1999).

It is submitted that claims 3-5 are not obvious under 35 U.S.C. § 103(a) in view of GOOSEN and MATHIOWITZ when each is taken alone or in combination. Allowance of claims 3-5 is respectfully requested.

Claim 7 is rejected under 35 U.S.C. § 103(a) as being obvious in view of GOOSEN in view of Mathiowitz et al., J. Controlled Release (1987) 5: 13-22 ("MATHIOWITZ II") It is respectfully submitted that claim 7 is not obvious in view of these references when each is taken alone or in combination.

The deficiencies of GOOSEN discussed above are reiterated hereat. Claim 7 is not rendered obvious in view of GOOSEN.

The deficiencies of MATHIOWITZ, discussed above with respect to claims 3-5, apply equally as well to MATHIOWITZ II. GOOSEN employs a polymer system which is different than that of MATHIOWITZ II. GOOSEN's carrier system, i.e., the semi-permeable membrane does not degrade in order to deliver the desired material, whereas MATHIOWITZ II has a carrier which degrades to achieve delivery. As the Examiner points out, GOOSEN "fails to teach a method of preparing the construct of claim 1 which comprises ... mixing at the **temperature of** about 0.5 [sic – 0.5] to 28° C..." (emphasis added)

whereas, MATHOIWITZ II teaches **Hot** – melt microencapsulation. The obvious is noted, namely Hot-melt is not –0.5 to 28° C.

MATHIOWITZ II employs hot to moderate temperature, not cold to about room temperature. In this regard, reference is made to MATHIOWITZ II at page 14, right hand column, first full paragraph, where it is stated:

> ... The molecules (drugs)were encapsulated as solid particles. The mixture was suspended in a non-miscible solvent that was **heated** 5° C above the melting point of the polymer... (emphasis added)

and to page 20, right hand column, bridging paragraph, to page 21, left hand column, line 3, where it is stated:

> ... The disadvantage of this approach is the **moderate temperature** to which the drug is exposed. One way to overcome this problem is to synthesize polymers with lower melting points ... Methods for microencapsulation that can be carried out at room temperature are being **explored** [not achieved], (emphasis added).

MATHIOWITZ II does not even hint at Applicants' invention as defined in claim 7.

There is no motivation to combine GOOSEN with MATHIOWITZ II. *In re Dembiczak, supra*. Even when combined, Applicants' invention as defined in claim 7 is not rendered obvious to one of ordinary skill in the art. Accordingly, allowance of claim 7 is respectfully requested.

Claim 8 is rejected under 35 U.S.C. § 103(a) in view of GOOSEN taken in view of MATHIOWITZ. It is submitted that claim 8 is not obvious in view of these references taken alone or in combination.

The deficiencies of MATHIOWITZ discussed above are reiterated hereat. Claim 8 is not rendered obvious from the teachings of GOOSEN.

The deficiencies of GOOSEN discussed above are reiterated hereat. Claim 8 is not rendered obvious from the teachings of MATHIOWITZ. In this regard, it is also to be pointed that claim 8 defines Applicants' invention in terms of forming a **solution** of polymer and medicament, whereas MATHIOWITZ teaches a method of forming a **suspension** of polymer and medicament (MATHIOWITZ, at page 758, third paragraph).

Again as discussed above, why would one of ordinary skill in the art combine two references which (1) employ different polymer systems, (2) utilize different delivery mechanisms (through a semi-permeable membrane as compared to release by hydrolysis degradation of the polymeric carrier), (3) prepare a construct utilizing a temporary capsule and forming a membrane thereabout (GOOSEN, Col. 2, line 61, to Col. 3, line 13) as compare to preparing a construct using a **variation** of a solvent removal technique (MATHIOWITZ, page 758, third paragraph).

There is no motivation to combine GOOSEN and MATHIOWITZ, except by a hindsight view provided by Applicants' invention. *In re Dembiczak, supra.*

Claim 8 is not obvious in view of GOOSEN combined with MATHIOWITZ and allowance of this claim is respectfully requested.

Claim 9 is rejected under 35 U.S.C. § 103(a) as obvious over GOOSEN in view of MATHIOWITZ. It is submitted that claim 9 is not rendered obvious in view of these references taken alone or in combination.

The deficiencies of GOOSEN discussed above are reiterated hereat and claim 9 is not rendered obvious in view of GOOSEN.

The deficiencies of MATHIOWITZ discussed above are reiterated hereat. MATHIOWITZ does not reveal the polymer system of the construct claimed in claim 9, much

less how to make such claimed construct. Claim 9 is not obvious to one of ordinary skill in the art in view of MATHIOWITZ.

There is no motivation to combine GOOSEN with MATHIOWITZ and such combination for purposes of 35 U.S.C. § 103(a) is improper. *In re Dembiczak, supra.*

Allowance of claim 9 is respectfully requested.

Claim 10 is rejected under 35 U.S.C. § 103(a) as being unpatentable over GOOSEN in view of MATHIOWITZ et al., J. Appl. Polymer Sci. (1992) 45: 125-134 ("MATHIOWITZ III"). It is respectfully submitted that claim 9 is not rendered obvious under 35 U.S.C. § 103(a) in view of these references when each is taken alone or in combination.

The deficiencies of GOOSEN discussed above are reiterated hereat. Claim 10 is not rendered obvious in view of GOOSEN.

As with the other references authored by Mathiowitz et al., discussed above, MATHIOWITZ III reveals polyanhydride polymers. MATHIOWITZ III does not even hint at the polymer system defined in claim 10. Claim 10 is not rendered obvious under 35 U.S.C. § 103(a) in view of MATHIOWITZ III.

The combination of GOOSEN with MATHIOWITZ III is improper for purposes of 35 U.S.C. § 103(a). These references (1) employ different polymer systems and (2) utilize different delivery mechanisms (passage through a semi-permeable membrane as compared to release by degradation). There is only a hindsight motivation to combine and thus the combination is improper. *In re Dembiczak, supra.* Allowance of claim 10 is respectfully requested.

Claims 11 and 12 are rejected under 35 U.S.C. § 103(b) as being unpatentable over GOOSEN in view of Steiner et al., U.S. Patent No. 6,071,497 ("STEINER"). It is respectfully

submitted that claims 11 and 12 are not rendered obvious in view of these references when each is taken alone or in combination.

The deficiencies of GOOSEN discussed above are reiterated hereat. As indicated by the Examiner, GOOSEN "fail to teach a method of preparing the construct of claim 1 wherein particles of such construct are under 20 micrometers in diameter". Claims 11 and 12 are not rendered obvious under 35 U.S.C. § 103(a) in view of GOOSEN.

STEINER teaches the creation of particles that are designed with biodegradation properties which occur either as a result of pH change, as in the case of the diketopiperazines, or hydrolysis, as in the case of poly(hydroxy acids), or by diffusion of calcium ions out of the microparticle, as in the case of microparticles formed by ionic bonding of a polymer such as alginate, or by enzymatic action, as in the case of many of the polysaccharides and proteins. By ionic bonding and or enzymatic deactivation of the polymeric backbone, it must be understood that STEINER is creating high molecular weight, ordered, and chemically hindered species by specific chemical reactions, which are described in STEINER at Col. 2, line 57 to Col. 3, line 7. STEINER also teaches that these highly ordered polymeric species would degrade only when certain cationic species like calcium ions, or specific enzymes are present at the site of administration of the microspheres. The respective biochemical reactivities of these highly ordered polymers are not warranted in the subject invention as *in vivo* release is fortuitously based upon a physical mechanism and a slow intrinsic dissolution of the claimed construct in fluids in the peripheral lung.

Further, STEINER teaches that the alginate or polyphosphazines or other dicarboxylic polymerics hydrogel microspheres can be prepared by dissolving the polymer in aqueous solution, within which ionic hardening could be achieved such as taught, for example, by Salib,

et al., Pharmazeutische Industrie 40-111A, 1230 (1978) as this further modifies the surface of the microspheres by coating them with polycationic polymers such as polylysine, after fabrication, for example, as described by Lim, et al., J. Pharm. Sci. 70, 351-354 (1981). The Applicants's claimed invention fortuitously does not rely upon crosslinking of the alginate with calcium ions or particle outer surface modification with a polycation promoter such as polylysine for controlled medicament release to occur. A person of ordinary skill in the art would therefore conclude that distinctives as taught by GOOSEN and STEINER are irrelevant in the method claimed in claims 11 and 12.

As with the other combinations of references, previously discussed above, why would one or ordinary skill in the art combine GOOSEN with STEINER. These references deal with different polymer systems i.e., one which is not degraded or chemically modified (semi-permeable membrane) and one which is degraded or chemically modified. These references deal with different delivery mechanisms (selective membrane passage as compared to chemical modification and/or treatment to provide polymeric degradation). Additionally neither of these references hint at the claimed method of forming Applicants' defined polymeric construct which is not a semi-permeable membrane and does not need chemical modification to affect degradation thereof but merely is dissolved in the body of a patient being treated to produce dissolution controlled release of its entrapped or associated medicament.

Claims 11 and 12 are not rendered obvious by viewing GOOSEN and STEINER when each is taken alone or in combination. Allowance of claims 11 and 12 is respectfully requested.

Claims 13 and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over STEINER in view of Edwards et al., U.S. Patent No. 5,874,064 ("EDWARDS"). It is

respectfully submitted that these claims are not rendered obvious under 35 U.S.C. § 103(a) in view of these references when each is taken alone or in combination.

The deficiencies of STEINER, discussed above, are reiterated hereat.

EDWARDS reveals forming a polymer system which is different than that of Applicants, i.e., a biodegradeable polymeric system. Applicants' invention, as defined in claims 13 and 14, is directed to a method of forming a construct comprising a defined polymer which dissolves in the body of the patient being treated.

It is submitted that claims 13 and 14 are not rendered obvious in view of STEINER and EDWARDS when each is taken alone or in combination. Accordingly, allowance of claims 13 and 14 is respectfully requested.

The undersigned is hereby authorized to call the undersigned attorney on record "collect" on any matter connected with this application. The telephone number is 212-588-0800. In the absence of the undersigned attorney of record, the call will be accepted by any attorney empowered in this application.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW THE CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (Amended) A medicinal polymeric construct for treating a patient comprising a polysaccharide polymer, which dissolves in the body of said patient upon said treating with the construct, having a selected medicament entrapped therewithin which is released from the construct in a dissolution controlled manner to said patient upon said polymer dissolution.

Claim 8 has been amended as follows:

8. (Amended) A method of preparing the construct of claim 1 which comprises, dissolving said polymer and said medicament in a solvent to form a solution; exposing said solution to a critical pressure and temperature while mixing with [a suitable] an anti-solvent to dry said solution to form the construct.

Claim 9 has been amended as follows:

9. (Amended) A method of preparing the construct of claim 1 which comprises, dispersing said polymer in a solution of said medicament to form a dispersion; subjecting said dispersion to a critical pressure and temperature while mixing with an [appropriate] anti-solvent to dry said dispersion to separate the construct after about 0.0001 to about 24 hours.

Claim 10 has been amended as follows:

10. (Amended) A method of preparing the construct of claim 1 which comprises, dissolving said polymer in a solution of said medicament to form a polymer solution and drying said polymer solution as a spray for about 0.1 to about 8 hours to form the construct.

Claim 11 has been amended as follows:

11. (Amended) The method as defined in claim 8 wherein said construct comprises particles [of such construct] which are [range from under 20 micrometers, to] under 10 micrometers in diameter.

Claim 12 has been amended as follows:

12. (Amended) The method as defined in claim 9 wherein said particles of such construct are less than about [under 20] 10 micrometers in diameter.

Claim 13 has been amended as follows:

13. (Amended) The method as defined in claim 10 wherein said construct comprises particles [of such construct] which are less than about 10 micrometers [to about 20 micrometers] in diameter.

Claim 14 has been amended as follows:

14. (Amended) The method as defined in claim 11 wherein said particles of such construct are less [range from under] than about [10] 5 micrometers [to about 20 micrometers] in diameter.